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INFLUENCE OF EXTRINSIC FACTORS ON THE CORONARY FLOW AND CLINICAL COURSE OF HEART DISEASE*

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THERE are a great many clinical observations associated with heart disease, and especially with angina pectoris, which are difficult to explain only on the basis of intrinsic anatomical changes in the coronary vessels alone, and can best be explained by the assumption of vasomotor changes in the caliber of the coronary vessels, decreasing the flow volume. Such an assumption of vasomotor changes is not new, and has been made by a great many men at many times. I would like here to review some of the experimental and clinical evidence indicating that such a decrease in flow may occur in response to autonomic stimuli of various origins, and that such decreases in coronary flow from extrinsic factors may produce the same disproportion between blood supply and blood needs, as do intrinsic anatomical changes in the vessel walls, which restrict the coronary flow when additional demands are made upon it.

I am not unmindful of the importance of the intrinsic factors. The point which I wish to make is this, that both intrinsic and extrinsic factors are valent in the restriction of coronary flow in proportions which

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vary in different cases. But the intrinsic factors are not reversible, and the conditions imposed are permanent, and must be compensated for in various ways by various means. The extrinsic factors are reversible and their influence may be lessened or may be obviated altogether.

It is not necessary to enter into a discussion of the nervous control of the coronary vessels. I think that it may be assumed as rather generally accepted that the vagus nerve exerts a tonic vasoconstrictor effect upon the coronary vessels, varying in degree with different physiological conditions, and that vasoconstrictor impulses are carried by the vagus. In like manner, it may be assumed that vasodilator impulses are carried through the sympathetic fibers, and that there is also some degree of vasodilator tone present in the vessels.

Anrep,[1] in 1926, described a reflex vasoconstriction of the coronary arteries consequent upon increased intracephalic pressure. The pathway for this vasoconstrictor impulse was through the vagus. Stella[2] and others confirmed this, and showed that this was mediated through the carotid sinus.

Clinically, attacks of angina pectoris or of paroxysmal dyspnea are seen to occur occasionally when the blood pressure reaches a point higher than that usual for the individual. That the attacks are not always due to an increase of the heart's work with the increased pressure, would seem to be indicated in the cases reported by Lewis,[3] in which the pain came on at a certain high level of blood pressure, and was relieved by the coronary vasodilator action of nitroglycerin, even though there was no fall in pressure.

The increased tendency to anginal pain following meals is a frequent clinical phenomenon. The symptoms may be explained in part by the increased work demanded of the heart during the earlier periods of digestion. This does not explain, however, why the pain is so frequently relieved by belching gas, or why it occurs at one time and not at another in the same person, under the same conditions. Anginal pain is very frequent also in hiatus hernia. The pain is more apt to occur when the herniation is present and is less apt to occur when the hernia is reduced.

That the anginal pain in these cases is due to a reflex vasoconstriction of the coronary arteries, is shown by the work of Dietrich and Schweigl in 1931, working with von Bergmann.[4] Distention of the stomach in the dog caused a marked decrease in the coronary flow, and this was espe-

cially so if the distention was at the esophageal hiatus. This decrease in flow did not occur after atropine, or if the vagi were sectioned. Fenn, LeRoy and I[5] repeated this work, with similar results. We further confirmed these results in the unanesthetized dog by distention of the stomach before and after atropine after a Rein stromuhr had been previously placed upon a branch of the coronary artery. Also, if the free abdominal cavity were distended with air, we again obtained a decrease in coronary flow, but not after vagotomy or atropine.

We obtained clinical confirmation of these experiments, using the method of Levy,[6] in which anginous patients are asked to breathe a low oxygen mixture until the first symptoms of anginal pain appear, when the patient is switched to straight oxygen and the attack ceases at once. If the patient breathed this low oxygen mixture after a meal, the pain came on sooner than it did in the control experiments done upon an empty stomach. If atropine was administered before the meal, the pain on a full stomach came on no sooner than it had originally in the control experiments. However, there were two groups of these patients in whom the time appearance of the pain was deferred by atropine. In some of them, the pain after a meal and after atropine came on at the same time as it had in the control experiments. In some others it took a longer time for the pain to occur after atropine than in the control, even though the experiment was done upon a full stomach. This would seem to indicate that in this second group, in which the pain did not occur as soon as in the control, the pain was due not only to intrinsic changes in the vessel walls, but to an extrinsic increase in vagal tone which had been released by the atropine. We then did another series of experiments upon the same patients, with an empty stomach, exactly as in the control experiments, but here we administered atropine before the experiment. In these experiments, the patients fell into the same two groups. One group experienced pain after the same time interval as in the control experiments, without the atropine. This group was the one in which there was more clinical reason to assume intrinsic changes in the vessel walls. The other group did not experience any symptoms for a longer time than had been noted in the control experiments, and a still longer time than that noted in the experiments done after a full meal. This group was that in which there was more clinical reason to assume the presence of an increased vagal tone, in addition to intrinsic vascular changes.

There is no need to emphasize the clinical importance of these observations in view of the frequency of anginal pain after meals. Master[7] has also shown the greater incidence of coronary thrombosis after meals.

In the experiments upon dogs, it was noted that the decrease in coronary flow was more marked if the distention was at the cardiac end of the stomach, and especially if the distending bag were against or in the esophageal hiatus. While hiatus hernia is being diagnosed more frequently than before, there is reason to think that it is still underdiagnosed, and its importance not fully realized. In a series of one hundred and seven cases of anginal pain followed in the last two years, in forty-four patients examined roentgenologically, there were eighteen or 17 per cent who showed a hiatus hernia. Just what the figure would be for a control series, I do not know, as I know of no control series to which some objection could not be made. But I do know that in the series of patients with angina pectoris and hiatus hernia, under our observation, there was a very clear history indicating the influence of the herniation upon the occurrence of the anginal pain, and that medical management of the hernia was apparently a factor in relief of these patients. It is to be emphasized that the anginal pain in hiatus hernia is not merely "anginalike," but that it is a real anginal pain resulting from an insufficient blood supply to the heart muscle.

Dr. Van Dellen has a case of hiatus hernia under observation at present, in which the electrocardiogram is normal when the herniation is not present, but in which there is a typical coronary curve present when the hernia occurs.

Hiatus hernia may also induce attacks of paroxysmal auricular fibrillation. I have seen two such cases in the last two months, in which there was very clear evidence that the attacks came on with the incidence of the hernia, and disappeared when the stomach slipped back into place. There is every reason to think that this occurrence is mediated through the vagus.

von Bergmann showed also that coronary vasoconstriction resulted from stimuli having their origin in the esophagus. We have all of us seen patients in whom attacks of angina were precipitated by the act of swallowing. Anginal pain is also found associated with diverticula of the esophagus and diverticula at the cardiac end of the stomach. Weiss and Ferris[8] reported a case in which Stokes-Adams attacks were brought

on by the act of swallowing. They showed that it was a vago-vagal reflex, and that it was clinically relieved by atropine.

Attacks of angina pectoris associated with gall bladder disease have been reported by several authors. Schwartz and Herman[9] reported that in most cases of gall bladder disturbance associated with cardiac symptoms, the heart symptoms were less after the operation. Fitz-Hugh and Wolferth[10] also showed an amelioration of the cardiac symptoms after gall bladder surgery, and showed that electrocardiographic changes tended to return to normal.

Some experiments which Fenn, LeRoy and I did upon the anesthetized dog could be interpreted as showing that there was a decrease in coronary flow upon distention of the gall bladder, but we did not consider our results wholly conclusive. In the last few weeks, Sheridan and I have repeated these experiments upon the decerebrate dog, and have obtained definite evidence of a decrease in coronary flow upon distention of the gall bladder, or distention or irritation of its ducts. This reflex did not occur after vagotomy, or after atropine.

It is possible, also that stimuli resulting from other abdominal conditions may initiate vasoconstrictor effects upon the coronary arteries. Angina pectoris is frequently associated with duodenal ulcer, a spastic duodenal bulb, a spastic colon, or diverticulosis of the colon. One can not be certain, however, how much the anginal symptoms are a result of reflexes arising from the abdominal conditions, and to what extent the anginal pain results from a common tendency to respond more readily than normal to vagal influence, or to the same lack in both cases of some inhibitions of this reflex, from higher centers. Experimentally, Smith and Miller[11] have shown that vagal reflexes may originate in the colon, as well as in the gall bladder. The part played by the gastrointestinal tract in producing cardiac symptoms has recently been reviewed by Morrison and Swalm.[12]

Danielopolu[13] long ago considered that stimuli arising from intrathoracic conditions might institute reflexes which decreased coronary flow, and such a thesis was in part the basis for operative interference to interrupt that reflex.

Scherf and Schönbrunner,[14] in 1937, published observations showing that lung emboli were associated with anginal pain, and similar observations have been reported since. DeTakats, Beck and Fenn[15] presented evidence indicating that there was a coronary vasoconstriction asso-

ciated with the lodging of an embolus in the pulmonary vessels, and that this was a reflex mediated through the vagus. The cases of heart block associated with pulmonary emboli reported by Kauffmann[16] would indicate vagal stimulation by the embolus. DeTakats and his co-workers have also shown a constriction of the pulmonary vessels, and of the bronchi, associated with pulmonary embolism.

DeTakats and Jesser[17] consider that such coronary vasoconstriction is the cause of death in many cases of pulmonary embolism, and that death is not always due to asphyxiation or right heart failure or incomplete venous return to the heart. Acting upon this hypothesis, and treating cases with atropine and papaverine, or atropine and aminophylline intravenously, resulted in a decrease in the death rate in their cases of pulmonary embolism from 82 per cent to 13 per cent.

Even more important from a clinical standpoint, is the work of Manning, McEachern and Hall,[18] showing that when a coronary artery of the dog is ligated, there is a reflex vasoconstriction of the other coronary vessels. When a coronary artery of the dog was ligated under full anesthesia, there was a very low mortality. But if the ligature were placed about the vessels under full anesthesia and not tied until several hours later, after recovery from the anesthetic, there was a very high mortality. But if the vagi were cut or atropine administered before the artery was ligated in the unanesthetized dog, the mortality remained at the same low level as when the artery was tied in a dog in which the reflexes were abolished by full anesthesia. In some work that has not as yet been published, LeRoy, Gilbert and Fenn have shown that when the artery is ligated, the mortality is not only less with atropine, but even less if a purine-base vasodilator is used.

These observations of Manning, McEachern and Hall are of very great clinical importance in the management of coronary thrombosis. Making use of these observations, we have very greatly reduced our mortality in early cases of coronary thrombosis, by the immediate administration of atropine and aminophylline. In addition, it must follow that if this secondary vasoconstriction was obviated, the infarct would be smaller and the myocardial damage less, with a better recovery and less loss of function. Recovery has been more rapid and more uneventful in our cases, than previously.

What we have said so far has concerned only reflexes mediated through the vagus. There are also reflexes mediated through the sym-

pathetic, which are constantly active, and tend to increase the coronary flow in response to increased needs. Failure of this normal vasodilator mechanism of the sympathetic, or an inhibition of the sympathetic, would necessarily result in an inability of the heart to adapt itself to its changing needs.

It has been known for a great many years that the pulse rate could be slowed by stimulation of the nasal mucous membrane in animals, and that this effect could still be obtained by the same stimulation after vagotomy or atropine, or both. The blood pressure might rise, or might remain unchanged. This can only be explained by assuming an inhibition of sympathetic tone.

These observations would seem to afford a possible explanation of the attacks of angina pectoris which occur when an anginous subject suddenly breathes cold air through the nose. Such attacks may even be fatal.

In order to determine if there might be a loss of sympathetic vasodilator tone in the coronary arteries, associated with what appears to be a sympathetic inhibition, experiments were done upon the decerebrate dog, in which the coronary flow was measured.[19] Upon stimulation of the nasal mucous membrane with cold water, or chloroform vapor, a decrease in coronary flow was observed, associated with a slowing of the pulse, and a rise in blood pressure. After vagotomy, or atropine, the same event occurred.

If ergotamine tartrate was administered to dogs in doses corresponding to those used clinically, for its sympathetic inhibitor effect, the same sequence of events occurred as was seen upon stimulation of the nasal mucous membrane. Vagotomy or atropine did not abolish this effect.

When experiments were done upon anginous subjects, inducing anginal pain by means of breathing a mixture low in oxygen, the pain was found to appear much sooner if ergotamine were administered before starting the experiment.

The experiments with ergotamine tartrate upon the dog, and upon the anginous subject are open to the objection that in each case the ergotamine tartrate may have exerted a direct vasoconstrictor action upon the coronary vessel walls. Katz[20] has shown such an effect in the empty beating heart of the dog and we have confirmed it. But I am not at all certain that these observations altogether settle the question of a direct action upon the vessel, and I would feel that much further work

is necessary. The curves representing the effects of stimulation of the nasal mucosa, where there is no question of any drug acting upon the vessel, and those obtained after the administration of ergotamine, are identical, and I would feel that this is of some significance.

The effect of tobacco upon the induction of anginal attacks has been commented upon frequently. Huchard[21] in his chapter upon Toxic Angina Pectoris, had a great deal to say about the effect of tobacco in causing attacks. Wilson and Johnston[22] recently reported a series of cases with what would seem very clear evidence that the anginal attacks were caused by a vasomotor narrowing of the coronary arteries, precipitated by the smoking. Hobbs, working upon this problem, has found two cases where the electrocardiographic changes did not occur after atropine.

I spoke earlier of the possibility that vasomotor restriction of coronary flow, oft repeated over long periods of time, might eventually result in permanent degenerative changes in the heart muscle consequent upon temporary decrease in blood supply. Blumgart and his fellow-workers[23] have shown that arrest of the blood flow for as short a period as one minute in a single coronary artery led to electrocardiographic changes indicating anoxemia of the muscle. Arrest of the flow for from 25 to 45 minutes produced histological changes in the muscle.

Hall, Ettinger and Banting[24] have shown that prolonged stimulation of the vagus, continued over several months of time, produced changes in the heart muscle of the dog, comparable to chronic clinical degenerative changes in man. Intrinsic changes in the vessel walls of the dog's heart did not occur to any significant degree. It would seem very reasonable to assume that similar changes occur clinically in man, or as a result of repeated extrinsic factors restricting the coronary flow for varying periods, over long time intervals.

The experiments of Hall and his associates were performed upon dogs with normal heart muscles and normal vessels. When the heart of man is hypertrophied from any cause, whether as a result of previous valvular damage, or as a result of hypertension, there is an increased bulk of heart muscle without a proportionate increase in blood supply to provide for the increased needs. In such hearts, with a blood supply already insufficient, or barely sufficient, and possibly with intrinsic vascular changes, a further restriction of coronary flow because of extrinsic

factors may produce serious changes much more rapidly and much more certainly than in a normal heart.

I am sorry to have burdened you with so long a discourse, but even then it is too brief and incomplete to show adequately the importance of the extrinsic factors which tend to decrease the coronary flow. I hope that what I have said has carried some small degree of conviction as to the importance of these factors in diagnosis and therapy.

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